Testicular Vascular Lesions

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To my dearest daughter Natalia and the long-awaited grandson Jorge

To Maytechu for the happy reunion

Manuel Nistal

To my husband, Alvaro

To my children Álvaro, Teresa, and Javier

In memoriam, to my parents Antonio and Pilar

Pilar González-Peramato

Preface

Pathology has been fundamental to the advances in diagnostic procedures that have facilitated treatment individualization. The contribution of pathologists in both the tumoural and non-tumoural field of the testis has been very important. While the information provided by histological studies continues to be the basis for classifying neoplasms, in the non-tumoural field, testicular biopsy has been progressively marginalized over the last decades. Genetics, molecular biology, and the application of other techniques have been incorporated into the study of the patient. The most surprising thing in these studies is that their results always relate them with possible testicular lesions, based on the classic descriptions of those lesions, but the existence of which in that specific patient is unknown. The type of testicular lesion cannot be detected by karyotype, whether in the field of congenital anomalies, nor is it alone a determinant in the reproductive capacity of an infertile male. Molecular studies can pinpoint the genetic cause of an anomaly, but the expression of a genetic defect can be variable and therefore cannot be used to predict the functional capacity of the testis. The same can be said in many cases of hormonal determinations. Each contributes value to the diagnosis, but it is only the pathology that allows us to know what is happening inside the testicle, the actual nature of the lesions, their progressiveness, or to suggest a treatment.

The readers will find in this book a different viewpoint of approaching the nature of some testicular lesions: the study of vascular lesions. Most of the references in the scientific literature in this field are reduced to citing testicular torsions and varicocele. Without underestimating the fact that the studies focus on the seriousness of the loss of a testicle due to torsion of the cord or the negative impact of varicocele on fertility, the field of vascular pathology is much broader and the references to the different processes are scarce.

This book contains the testicular pathology produced by lesions associated with arterial, venous, and lymphatic vessel lesions in an orderly fashion. Sometimes, as is logical, the alterations are purely testicular, in others, the majority, the testicle is the target organ of systemic pathologies. The first ten chapters are dedicated to arterial pathology, the following five to venous pathology, and the final four to pathology of the lymphatic vessels.

In the review of testicular specimens in our files, previously undescribed vascular, arterial, venous, and lymphatic vessel lesions have been observed and have been incorporated in the respective chapters. Whether they are mere histologic findings or represent entities with a certain category is left to the readers' consideration.

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Finally, we wish to acknowledge C.F. Warren for her help to improve the English grammar and syntax of our manuscripts to transform them into readable documents.

Contents

Part I

Arterial Pathology: Introduction

The high frequency of abdominal cavity surgery has markedly increased the importance of knowing/understanding the anatomy of the testicular artery in order to avoid irreversible testicular lesions [1]. The testicle is irrigated by the testicular artery, which originates from the anterolateral aspect of the abdominal aorta at the level of the second lumbar vertebra, 2.5–5 cm caudal to the origin of the renal artery. It descends retroperitoneally obliquely in front of the psoas muscle. Before crossing the deep inguinal ring, it crosses the genitofemoral nerve, ureter, and the inferior part of the external iliac artery before joining the spermatic cord and reaching the testicle. But, it is not uncommon for it to originate from other arteries, such as the main artery of the kidney or the accessory renal artery, the middle adrenal artery or one of the lumbar arteries, the common or internal iliac artery or even the superior epigastric artery [2–4]. Exceptionally, it can be double and each arm even has a different origin or even be missing, or may be absent, in which case the testicular vascularization will proceed from the vesical or prostatic arteries. Variants in its course are also important, such as running posterior to the inferior vena cava or forming an arch over the renal pedicles on both sides [5, 6]

The testicular artery descends within the spermatic cord surrounded by several venous, lymphatic, and nervous trunks (Fig. 1). Along the spermatic cord, it gives the superior and inferior epididymal arteries, which usually arise from a common trunk, as collaterals. Before reaching the testicle, the testicular artery bifurcates into an anterior/superior and posterior/inferior branch. Although the testicular artery is the main source of blood supply to the testicle, anastomoses with the deferential and cremasteric arteries are frequent (Fig. 2).

Before reaching the lower pole of the testicle, the testicular artery penetrates the tunica albuginea and divides into capsular arteries, which are situated in the tunica vasculosa, leading tortuously from the inferior pole to the superior pole of the testicle, along its anterior aspect. At different levels of this course, they give rise to arteries that follow the interlobular conjunctival septa towards the rete testis. These branches are known as centripetal arteries. Along their course, the centripetal arteries change direction, and, with numerous branches, they head towards the albuginea (recurrent rami); these are the centrifugal arteries from which the arterioles of the testicular intersti-

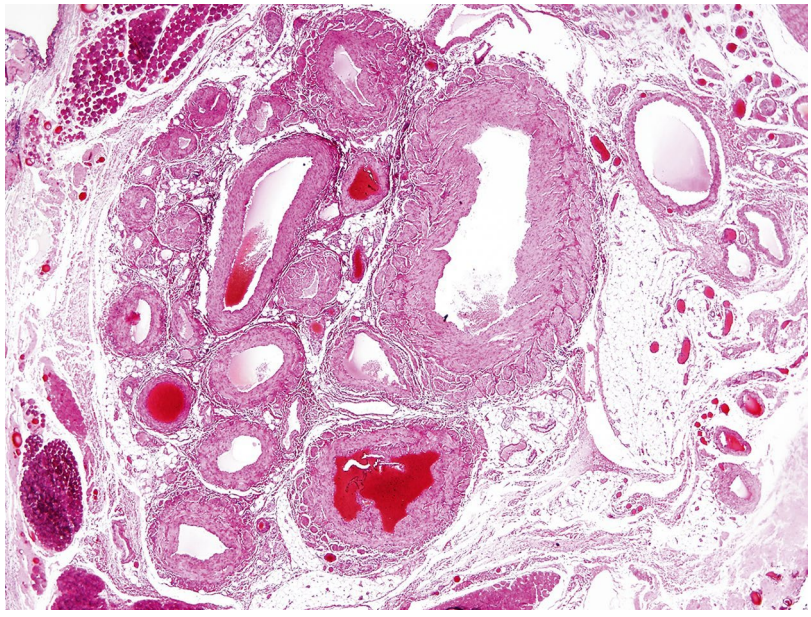

Fig. 1 Cross section of the spermatic cord. The testicular artery is located in the central part and surrounded by several veins. In contrast to the thin wall of the artery and its small branches, the thick wall of the veins with longitudinal smooth muscle bundles in the adventitia stands out

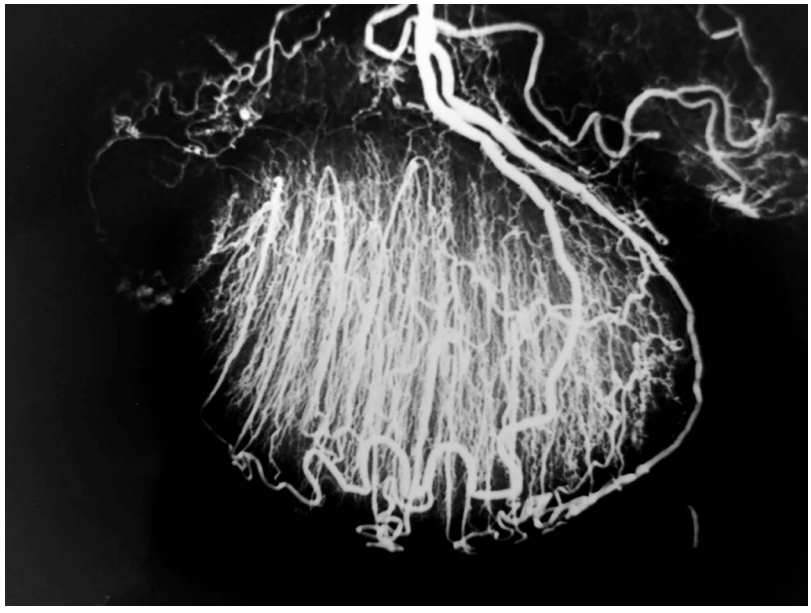

Fig. 2 The two branches of the testicular artery lead to the inferior pole. They pierce the albuginea and, after a sinuous course under the albuginea, give rise to the centripetal arteries

tium arise. Before changing direction again, the centripetal arteries give rise to fine spiral or corkscrew arteries that reach the testicular mediastinum (Figs. 3 and 4).

Arterioles give rise to capillaries that extend through the interstitium between Leydig cell clusters (forming intertubular capillaries) or in the proximity of the tunica propria (forming peritubular capillaries). The former are of a continuous type, their cells show little pinocytosis, strong adherent fascia-like junctions, and have low permeability. The endothelial cells of the peritubular capillaries are partially fenestrated.

The testicular artery or its branches can be affected in the same way as those of other territories in different pathologies. Vasculitis lesions can be observed in autopsy studies and sometimes in surgical specimens. Following the nomenclature adopted for the classification of vasculitis, most vasculitis seen in the testis, epididymis and spermatic cord are small vessel vasculitis, although in some cases medium-sized vessels may be involved. Testicular vasculitis can be secondary or primary (idiopathic) [7]. Among secondary small vessel vasculitis, ANCA (anti-neutrophil cytoplasmic antibody)-associated vasculitis such as microscopic polyangiitis, granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, Behçet's disease, and Cogan's syndrome stand out. Immune complex-mediated small-vessel vasculitis such as rheumatoid arthritis and systemic lupus erythematosus, IgA (Henoch-Schönlein) can also occur.

Vasculitis associated with bacterial, viral, or paraneoplastic diseases or with drugs is also seen in the testis [8]. Structural lesions like testicular artery aneurysms or arteriovenous fistulas are rare. Other vessel lesions such as arte-

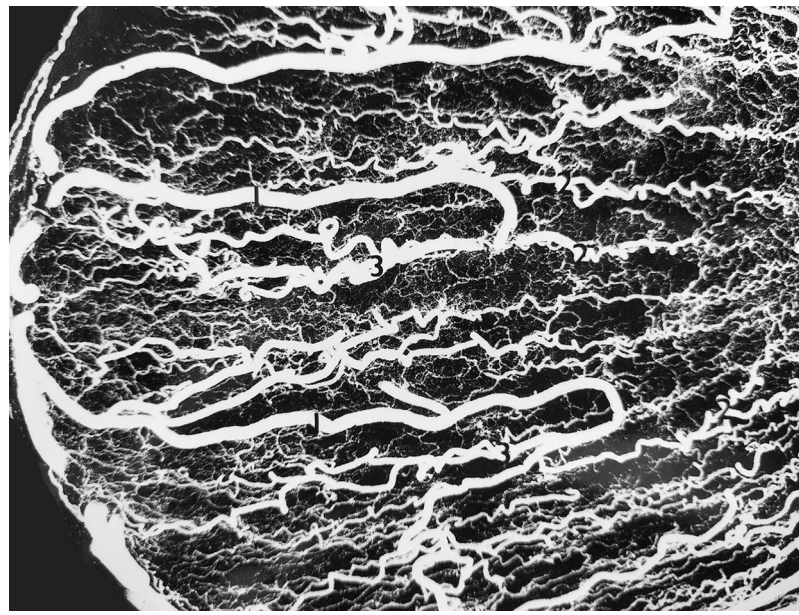

Fig. 3 Centripetal arteries (1) follow the interlobular septum, as they approach the testicular mediastinum they give rise to highly spiralized arteries (2). Along their course, the centripetal arteries give collaterals to the centrifugal arteries, which are directed towards the periphery of the parenchyma they are irrigating

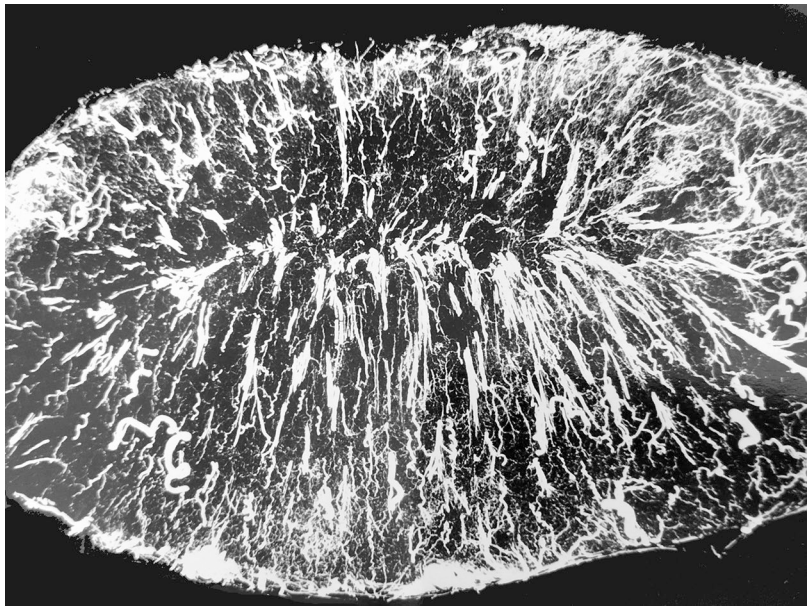

Fig. 4 In this section, close to the testicular mediastinum, note the bending of the centripetal arteries which transforms them into the centrifugal arteries that spread towards the albuginea

riosclerosis, atherosclerosis, arteriolosclerosis, arteriosclerosis obliterans (ASO) Mönckeberg medial calcific sclerosis, thromboembolism, or thromboangiitis obliterans (TAO) appear with age.

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1 Large- and Medium-Sized Vessel Systemic Vasculitis with Testicular Involvement

1.1 Giant Cell Arteritis (Temporal Arteritis)

Giant cell arteritis, also known as temporal arteritis, is the most common autoinflammatory and autoimmune vasculitis affecting medium and large vessels. The incidence of the disease increases from the age of 50 years and peaks at between 70 and 79 years of age [1]. The highest incidence is observed in individuals of Scandinavian descent, specifically in Norway with an annual incidence of 32.8 per 100,000 in inhabitants over 50 years of age [2]. The aetiology is unknown although it is related to immunological processes triggered by inflammatory or environmental agents [3].

Granulomatous vasculitis like those affecting the temporal artery has been observed in other locations such as the heart, renal arteries, gallbladder artery, and in veins of the lower extremities. The vessels of the spermatic cord and testis may be affected in the context of generalized disease [4]. The clinical presentation is that of a testicular mass simulating an orchitis [5] or a malignant tumour [6]. The lesions are formed by a granulomatous reaction with abundant $CD4^+$ T cells, macrophages, and giant cells preferentially located in the intima of the vessels in relation centred in the internal elastic lamina, which has a fragmented appearance [7].

Another granulomatous vasculitis, with a histological image that is similar to giant cell arteritis, is Takayasu's disease [8], but this disease has clear differences from classical giant cell arteritis in genetics, epidemiology, pathogenic mechanisms, response to treatment and complications of treatment [9]. Testicular involvement developed in the course of the disease in a 7-year-old patient with Takayasu disease [10].

1.2 Polyarteritis Nodosa (PAN)

Polyarteritis nodosa (PAN) is a form of multisystem necrotising vasculitis affecting small- and medium-sized muscular arteries of the kidney, liver, heart, adrenal glands, gastrointestinal tract, joints, spleen, lungs, and central nervous system without accompanying glomerulonephritis that spares arterioles, capillaries, and venules [11]. The annual incidence is estimated at 0.7/100,000, preferentially affecting males between the fourth and sixth decade of age. PAN accounts for 9% of vasculitis in childhood, ranking third behind IgA vasculitis/Henoch-Schönlein purpura (IgAV/HSP) and Kawasaki disease [12].

In PAN, both the testis and epididymis are affected [13]. The estimated frequency in autopsy series is 60% and 86%. Only 2–18% of the cases are symptomatic [14]. In 10% of cases, epididymal and/or testicular involvement is the first manifestation of systemic vasculitis. In these cases, the clinical presentation may be orchitis, epididymitis, torsion or testicular tumour [15, 16].

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The definitive diagnosis of the condition is histological. The testicle or epididymis often shows arterial lesions at different evolutive times (fibrinoid necrosis, inflammatory reaction, thrombosis, or aneurysm), even in the same organ. Initially, the parenchyma shows more or less extensive areas of infarction followed by tubular sclerosis with interstitial fibrosis (Figs. 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6).

The aetiology of PAN is unknown, and most cases are idiopathic. There are patients in whom it is associated with autoimmune diseases (rheumatoid arthritis, lupus erythematosus), infectious diseases (hepatitis B and C, HIV), or tumours. Three PAN patients with testicular involvement had an associated neoplasm (prostate adenocarcinoma, acute myelogenous leukaemia, hairy-cell leukaemia, and hepatocellular carcinoma). In

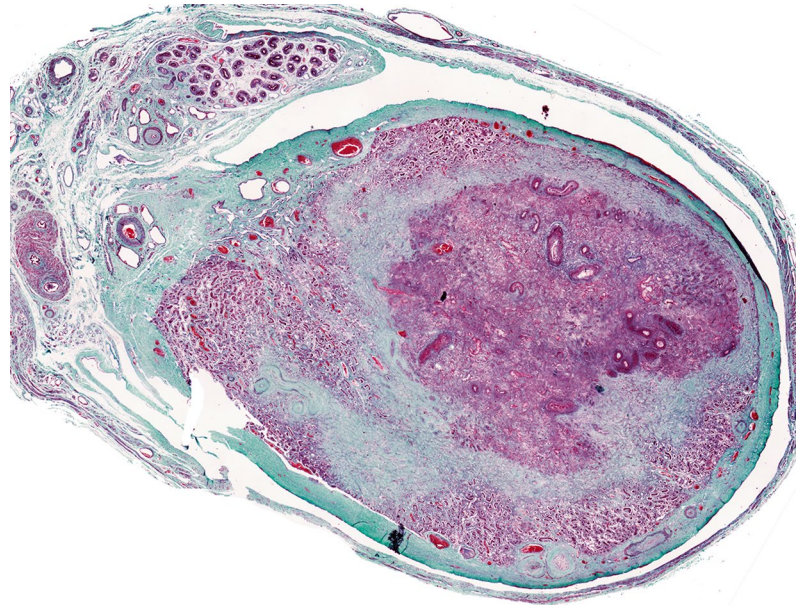

Fig. 1.1 Polyarteritis nodosa. Longitudinal section of testis, epididymis, and tunica vaginalis. The testicle has a central necrotic area surrounded by fibrous tissue. Preserved testicular parenchyma (Masson's trichrome) is visible only in the subalbuginea area

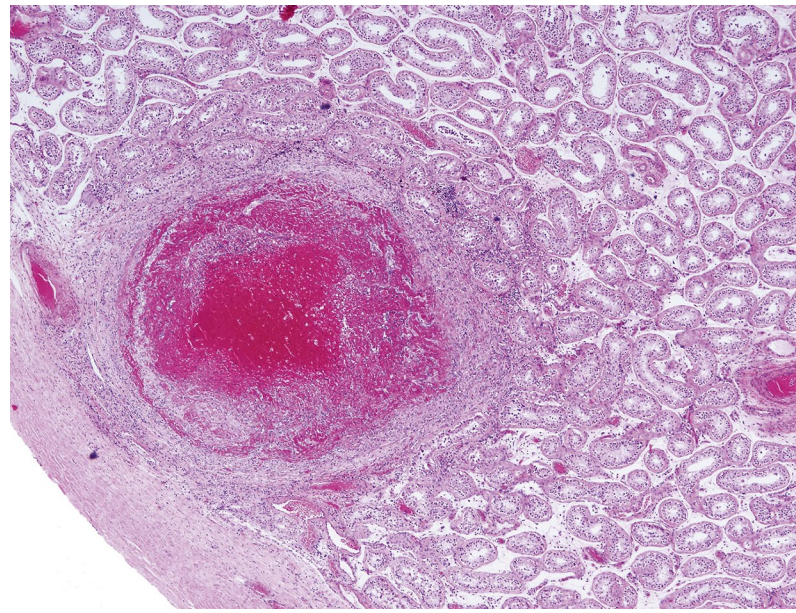

Fig. 1.2 Polyarteritis nodosa. Subalbuginea artery with partial necrosis of the wall and thrombosis. It is surrounded by an inflammatory infiltrate extending to the nearby seminiferous tubules. The remaining parenchyma is better preserved

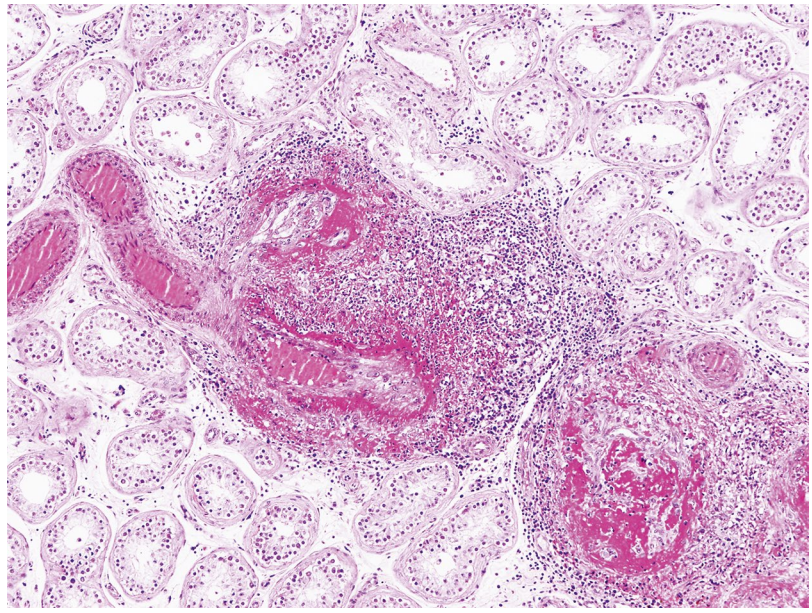

Fig. 1.3 Polyarteritis nodosa. Along an interlobular artery there are some normal segments and others with fibrinoid necrosis, thrombosis, and lymphoid infiltrates around them

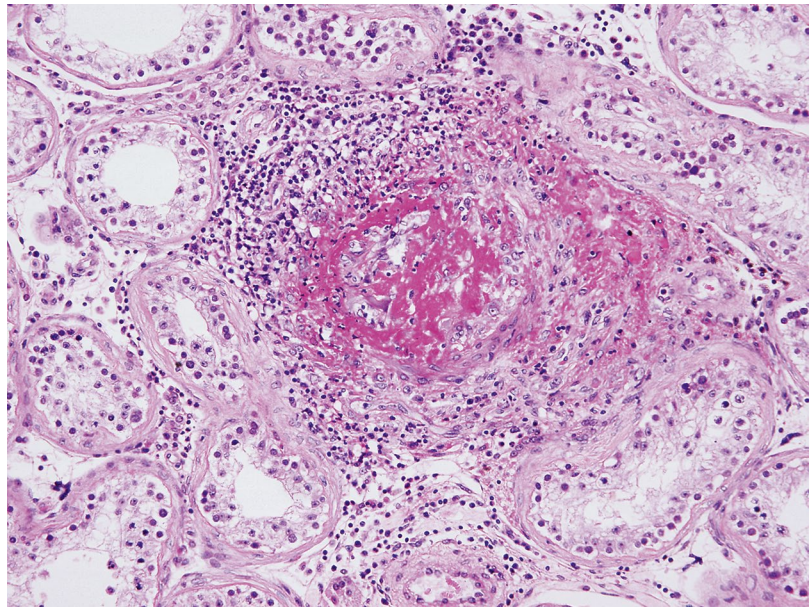

Fig. 1.4 Polyarteritis nodosa. Cross section of an intraparenchymal artery with extensive fibrinoid necrosis of the wall surrounded by lymphoid infiltrates. The seminiferous tubules have decreased calibre and a maturation arrest in spermatogonia

contrast to microscopic polyangiitis, Wegener's disease and Churg-Strauss syndrome, antineutrophil cytoplasmic antibodies (ANCAs) are not present in classic PAN [11].

A vasculitis that may be related to PAN is known as lymphocytic thrombophilic arteritis or macular lymphocytic arteritis [17]. This vasculitis has an indolent course and is accompanied by livedo racemosa or macular hyperpigmentation. It affects the small- and medium-sized arteries of the hypodermis and deep dermis and is characterized by the deposit of a thick fibrin ring in the intima and a dense infiltrate of mononuclear cells, mainly lymphocytes and some histiocytes, around the vessel. The presence of polynuclear neutrophils and eosinophils is residual. In rare cases, other organs can be involved, including the testis, resulting in bilateral testicular infarcts [18].

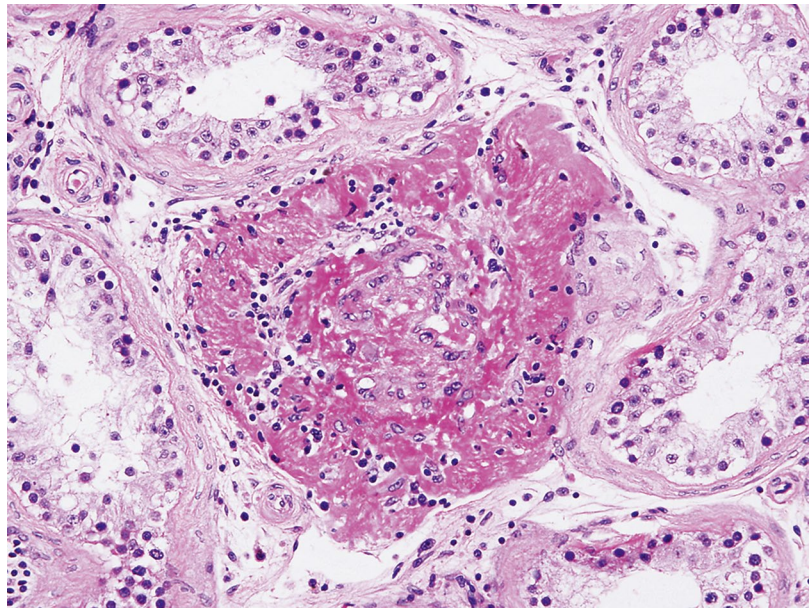

Fig. 1.5 Polyarteritis nodosa. Intraparenchymal artery with fibrinoid necrosis of all layers and partially recanalized thrombosis

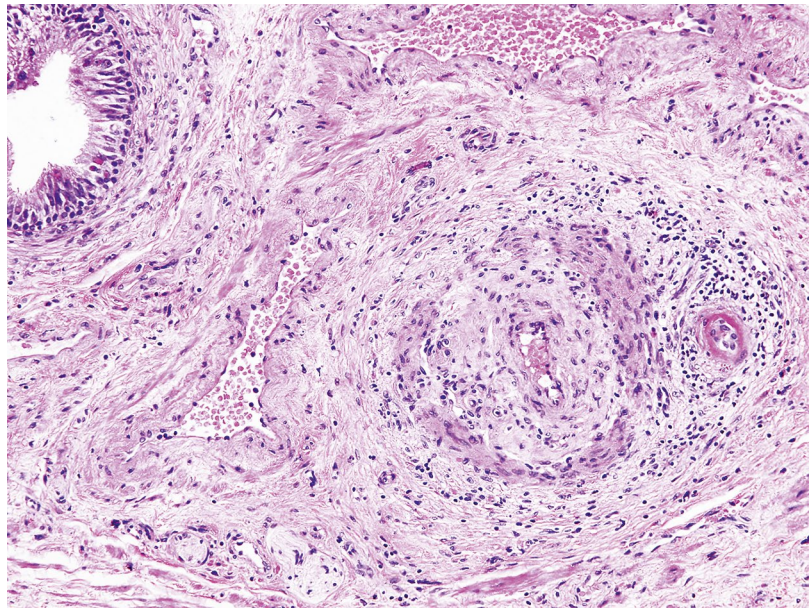

Fig. 1.6 Polyarteritis nodosa. The section of the epididymis shows an artery with luminal stenosis, discontinuous fibrosis of the media and adventitia with minimal lymphoid infiltrates that are interpreted as sequelae of the vasculitis. Next to the artery, an arteriole shows fibrinoid necrosis of the wall

1.3 Kawasaki Disease (KD)

This multisystem vasculitis preferentially affects children under 5 years of age with mucocutaneous lymph node syndrome. After 5 or more days with fever, patients develop most of the following symptoms: bilateral conjunctival injection, oral and upper respiratory tract mucosal changes (oedema, erythema) in the mouth and upper respiratory tract, polymorphous rash, oedema, and erythema of the extremities and cervical adenopathy [19]. Medium and small arteries are preferentially affected. KD is considered the most frequent cause of acquired coronary artery disease in children.

Testicular involvement is a rare complication. In most cases, it manifests simply as a hydrocele,

but in others, the clinical presentation is that of an acute scrotum [20, 21], which implies the need for a correct differential diagnosis among possible causes: torsion of the spermatic cord or testicular appendages, incarcerated inguinal hernia, orchio-epididymitis, testicular tumour, and acute idiopathic scrotal oedema. Treatment with immunoglobulin, aspirin, and prednisolone resolves scrotal swelling in most cases [20, 22].

The few histological studies, both on surgical specimens [23] and autopsies, have revealed a testicular arteritis or arteritis of the vessels of the spermatic cord [24, 25] that is morphologically indistinguishable from PAN [26].

1.4 Behçet's Disease

This systemic vasculitis clinically manifests as recurrent aphthous oral and genital ulcers, relapsing uveitis, and skin lesions (folliculitis, erythema nodosum-like lesions) and a positive pathergy test. Other frequently associated pathologies are arthritis, thrombophlebitis, and various neurological syndromes [27, 28]. It has a higher prevalence in countries along the ancient silk route extending from Japan to the Mediterranean and Middle Eastern countries than in northern European and North American countries and this may reflect a genetic predisposition as well as environmental triggering factors [29]. It preferentially affects individuals between 20 and 40 years of age.

There is a strong association between Behçet's disease and human leukocyte antigen (HLA) type B51 and HLA-12. Many patients with Behçet's disease carry the B5101 allele, so this may be a predisposing marker for the disease [30]. Exposure to an infectious agent would produce an autoinflammatory response in genetically predisposed individuals. The inflammatory mechanism, mediated by natural killer cells and heat shock proteins, gives rise to clinical manifestations through inflammatory repair processes in the blood vessels of the affected tissues.

In 40% of cases, the vascular tree is affected [27]. The main arteries affected are the large calibre arteries like the aorta, pulmonary artery, popliteal artery, femoral artery, subclavian artery and, less frequently, the common carotid artery. Arteritis is initially manifested by increased neutrophil emigration followed by occlusive-thrombotic and aneurysmal phenomena. The perivascular infiltrate is dominated by T, $CD4^+$ and $CD8^+$ lymphocytes and HLA-DR cells [31]. This occlusive vasculitis leads to infarcts or haemorrhages in the various affected organs. Both superficial and deep veins develop thrombophlebitis [32]. Inflammation of the vein wall is considered the hallmark of the pathogenesis of Behçet's disease [33]. Venous wall thickening is secondary to a process also initiated by neutrophilic hyperfunction, which produces reactive oxygen species (ROS). ROS cause endothelial dysfunction, necrosis, and platelet activation followed by thrombus formation [34].

Testicular and epididymal involvement simulates orchitis or epididymo-orchitis [35] and usually appears several years after the onset of the disease. It has a variable incidence related to the geographical area and age of the patients: 2% in France, 6% in Turkey, 12% in Greece, 31% in Iraq, and 44% in Russia [36]. The incidence of orchio-epididymitis is higher in adult (11.3%) than in young patients (7.7%). The duration of testicular symptoms is 1–2 weeks and is thought to be secondary to vasculitis. The involvement may be recurrent, and, in these cases, nodules are observed in the affected area. A complication, as with other vasculitis, is testicular infarction [37]. Patients with Behcet's disease very often develop AA-type amyloidosis, which has an unfavourable prognosis [38].

In some cases, the vasculitis resolves spontaneously, without treatment, or with analgesics alone, but most cases require the administration of colchicine and/or non-steroidal anti-inflammatory drugs. In more resistant cases, the additional use of corticosteroids is justified [36].

1.5 Cogan Disease

Cogan disease is a rare, multisystemic autoimmune vasculitis affecting large- and medium-sized vessels that predominantly occurs in children and young adults [39]. Initially described as an association of ophthalmologic (interstitial